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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,045	01/23/2002	Rose-Mary N Boustany	5405.225	9439
20792	7590	03/23/2004	EXAMINER	
MYERS BIGEL SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627			GOLDBERG, JEANINE ANNE	
			ART UNIT	PAPER NUMBER
			1634	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

# Office Action Summary

Application No.	Applicant(s)	
09/830,045	BOUSTANY ET AL.	
Examiner	Art Unit	
Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2004.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 8-10 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 8-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

1. This action is in response to the papers filed February 11, 2004. Currently, claims 1-6, 8-10 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.
2. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims or applicant's remarks.

### ***Priority***

1. This application is a 371 of PCT/US99/24695, filed October 21, 1999 which claims priority to provisional application 60/105,262, filed October 22, 1998.

### ***Drawings***

2. The drawings are acceptable.

### ***Claim Rejections - 35 USC § 112- Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-6, 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of claims

Claims 1-6, 8-10 are broadly drawn to methods of screening a subject for a proliferative disease risk factor, by detecting the presence or absence of upregulation of the CLN3 gene wherein the upregulation of the CLN3 gene in the subject is indicative of an increased risk of developing a proliferative disease. The claims broadly encompass screening any subject, including, but not limited to humans, dogs, cats, horses. Moreover, the claims are broadly drawn to any proliferative disorder which is defined in the specification to encompass any cancer, arthritis, asthma, fibrosis, for example.

The teachings of the specification and working examples

The specification teaches an analysis of breast cancer cell lines, colon cancer cell lines (Figure 9-12, page 7-8), melanoma cell lines, neuroblastoma cell line, glioma cell line and glioblastoma cell line. The specification teaches that the melanoma cell lines actually had “less CLN3 expressed” (page 8, lines 15-18). Each of these analyses was performed on cell lines. The specification fails to provide any evidence that a similar pattern of over-expression is present in actual tumor tissue. There is no evidence that the correlation between upregulation of CLN3 would be present in actual tissues. Moreover, in the analysis provided, not all of the cell lines were correlated in the same

manner with CLN3 expression. The over-expression of CLN3 in cancer cell lines is not sufficient evidence to enable one skilled in the art to determine that this nucleic acid would necessarily be over-expressed in primary tumor tissue as compared to non-tumor tissue.

The specification teaches that the term “proliferative disease” as used herein “refers to both cancer and non-cancer disease. The specification teaches that “illustrative non-cancer diseases include inflammatory and/or immunoproliferative disorders such as arthritis, fibrosis, asthma and allergies” (page 9, lines 26-30). Moreover, the specification teaches that cancers may include leukemia, soft tissue and bone sarcomas, neuroendocrine tumors, squamous carcinomas and adenocarcinomas (page 10, lines 1-10).

Moreover, the instant specification contemplates the use of the invention on animal subjects such as cats, dogs, and horses for veterinary purposes (page 10, lines 5-10). The instant specification fails to provide any analysis of the CLN3 genes for each of these species. Furthermore, the instant specification has not taught the CLN3 gene sequence for equine (horses). The skilled artisan would be required to obtain the CLN3 gene from the additional species prior to performing the screening method and determine whether an association exists.

The specification has no working examples of solid tumors in a representative number of proliferative disorders, as defined by the instant specification. While there are cell line examples for human cancers, there are no tissue working examples for allergies, fibrosis, arthritis and asthma in various species including dog, cat and horse. The unpredictability of the art and the state of the prior art

There is a great deal of unpredictability in the expression of nucleic acids as indicative of diseases. As noted by the instant specification, not every cell line acts in a concordant manner, see the melanoma cell line, for example.

Moreover, Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that “the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease.”

With regard to a specific nucleic acid, namely PARP, Chabert *et al.* (Int. J. Cancer: 53, 837-842 (1993)) compare PARP gene expression, enzymatic activity and quantities in 3 animal tumor cell lines in culture verses those transplanted into a compatible host, and found that, for “a given tumor cell line, marked differences exist in poly(ADPR)P gene expression and enzymatic activity between cultured cells and cells obtained from solid or ascitic tumors. Indeed, poly(ADPR)P gene expression, endogenous activity and amount are higher in exponentially growing cells than in *in vivo* tumors (p. 837, see also Fig. 1).” Chabert *et al.* further suggest that such discrepancies in enzymatic activity between cell culture and *in vivo* growth conditions exist because of differences in proliferation rates and/or environmental conditions (p. 841). Thus, before determining that a certain cell line is associated with a proliferative disease, the skilled artisan would be required to perform experiments to ensure there is a correlation.

The post filing date art further confirms the unpredictability of this area. Rylova *et al.* (Cancer Research, Vol. 62, pages 801-808, February 1, 2002) teaches that CLN3 mRNA is not overexpressed in either melanoma or pancreas cell lines (see Figure 1, page 803).

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this association to solid tumors from individuals rather than cell lines and to any proliferative disease.

#### Level of Skill in the Art

The level of skill in the art is deemed to be high.

#### Guidance in the Specification.

The teachings of the specification do not establish that one could actually detect upregulation or overexpression of CLN3 as an indicator of proliferative diseases in general, let alone in any proliferative disorder including arthritis, asthma or fibrosis in any species including but not limited to dogs, cat and horses. Rather the teachings of the specification asserts that CLN3 is expressed at higher levels in several cell lines, but not differentially expressed in other cell lines. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. While one could conduct additional experimentation to determine whether, e.g., expression of CLN3 might be associated with e.g., certain types of proliferative disease, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

The specification merely discloses upregulation of CLN3 in a few cell lines, not all cell lines, which are asserted to be cancer models. While the ordinary practitioner in this field is highly skilled, the evidence presented in the specification does not provide even a highly skilled practitioner means to overcome the limitations of evidence derived from cell lines and to make and/or use CLN3 as a method for cancer diagnosis and/or

detection with any reliability. As discussed by Dermer *et al.* and Chabert *et al.* the level of predictability between the activity of tumor cell lines and actual tumor tissue is very low, and thus practicing this invention would require unreasonable experimentation on the part of the practitioner to further screen actual tumor tissue to test for a connection between CLN3 over-expression and cancer.

However, as noted above, cell lines are not sufficient models for cancer. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of the claimed invention. However, the closest prior art does not provide support for the use of CLN3 expression as an indicator for all proliferative diseases, including cancers, asthma, arthritis, fibrosis etc. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between CLN3 expression and proliferative disease, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention. In light of the teachings in the prior art, and the general unpredictability concerning the activity of CLN3 in tumor cell lines versus actual tumor tissue, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

### Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the presence of a possible association between CLN3 in cancerous cell lines for humans, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art



recognized problems in the use of the cell lines. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define an association for screening a subject, the lack of guidance provided in the specification, and the absence of a working examples directed at subjects balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

### **Response to Arguments**

The response traverses the rejection. The response asserts that cell lines are in fact a sufficient model for the claimed invention. This argument has been reviewed but is not convincing because the objective evidence of record does not support this assertion made by applicant's attorney. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the sufficiency of cancer cell lines for the claimed invention must be supported by evidence, not argument. The objective evidence of Dermer and Chabert each teach that cell lines and tumors show marked differences in expression.

The response asserts that CLN3 sequence is highly conserved across species and submits that Rylova (a post filing date piece of art by the inventors) supports this assertion. This argument has been thoroughly reviewed, but is not found persuasive because the Rylova article is post filing date art. In the response applicants submitted a post filing date reference from the inventors of the instant application and that the filing of such a reference does not provide objective evidence of enablement of CLN3 overexpression in any subject, not limited to human or mouse. As provided in MPEP 2164.05(a) "Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987)."

Moreover, as provided in 716.02(g) "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the

guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Further, the instant publication was published approximately 3 ½ years after the filing date of the instant application. Moreover, even if mice were found to be enabled in 2002, there is no evidence that CLN3 genes were known for many subjects including dogs and horses, for example and that there would be a similar overexpression.

The response asserts that CLN3 is elevated in a variety of cancer cell lines. This argument has been thoroughly reviewed, but is not found persuasive because the specification teaches that the melanoma cell lines actually had “less CLN3 expressed” (page 8, lines 15-18). Thus, the attorney arguments do not appear to be in agreement with the instant specification. Furthermore, the post filing date art of Rylova teaches that melanoma and pancreas are not significantly overexpressed.

The response that the blocking of CLN3 in prostate cancer cells has been shown to increase apoptosis. This argument has been thoroughly reviewed, but is not found persuasive. To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. There is no evidence that at the time of filing that blocking of CLN3 would increase apoptosis. Thus for the reasons above and those already of record, the rejection is maintained.

### ***Conclusion***

#### **4. No claims allowable.**

Art Unit: 1634


5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
**Jeanine Goldberg**  
**Patent Examiner**  
March 22, 2004

  
**BJ FORMAN, PH.D.**  
**PRIMARY EXAMINER**